**REMARKS**

Claims 1, 3-5, 8, 9 and 12 are pending in the subject application. Applicant has hereinabove amended claim 8. Accordingly, upon entry of this Amendment, claims 1, 3-5, 8, 9 and 12 will still be pending and under examination.

In making these amendments, applicant neither concedes the correctness of the Examiner's rejections in the January 27, 2004 Office Action, nor abandons the right to pursue in a continuing application embodiments of the instant invention no longer claimed in this application. Applicant maintains that these amendments to claim 8 do not raise any issue of new matter, and that claim 8 as amended is fully supported by the specification as originally filed. Accordingly, applicant respectfully requests that this Amendment be entered.

In view of the arguments set forth below, applicant maintains that the Examiner's rejections made in the January 27, 2004 Office Action have been overcome, and respectfully requests that the Examiner reconsider and withdraw same.

**Rejection Under 35 U.S.C. §112, First Paragraph - Enablement**

The Examiner rejected claims 8, 9 and 12 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, according to the Examiner, while being enabling for

methods of preparing a human undifferentiated immortalized cell line by fusing with human primary post-mitotic cells immortalized rho$^-$ cell line fibroblasts that comprise a replicable nucleic acid vector that expresses SV40 large T antigen, and selecting for fused cells that (i) have a functioning respiratory chain, (ii) contain the replicable nucleic acid vector expressing SV40 large T antigen, (iii) are immortalized, and (iv) express one or more genes that are expressed specifically by the primary post-mitotic cells, the specification does not reasonably provide enablement for methods of preparing a human undifferentiated immortalized cell line that does not express SV40 large T antigen, and does not express one or more genes that are expressed specifically by the primary post-mitotic cells.

In response to the Examiner's rejection, applicant respectfully traverses.

Without conceding the correctness of the Examiner's position, applicant notes that amended claim 8 contains language which fully addresses the Examiner's stated concern. Thus, the claimed invention is enabled.

In view of the above remarks, applicant maintains that claims 8, 9 and 12 satisfy the requirements of 35 U.S.C. §112, first paragraph.

**Claim Rejections under 35 U.S.C. §102(b)**

The Examiner rejected claims 1 and 3-5 under 35 U.S.C. §102(b) as allegedly anticipated by Wang et al. (In Vitro

Cellular and Developmental Biology 27(1): 63-74, 1/1991; "Wang").

In response to the Examiner's rejection, applicant respectfully traverses.

According to M.P.E.P. §2131.01, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Thus, for Wang to anticipate the cell line of claims 1 and 3-5, it would have to teach each and every element thereof.

Wang fails to do this.

Claims 1 and 3-5 provide an immortalized human undifferentiated cardiomyocyte cell line wherein the cell line is produced by a method comprising the step of fusing a post-mitotic primary non-immortalized human cardiomyocyte with a human fibroblast, the fibroblast (a) having been treated with ethidium bromide; (b) comprising a replicable vector expressing SV40 large T antigen which confers immortality on a cell comprising same; and (c) being free of mitochondrial DNA.

The claimed cell line is not the same as the W1 cell line of Wang. In support of this position, applicant attaches hereto as **EXHIBIT 1** a Declaration of Mercy M. Davidson, Ph.D, the inventor named in the subject application. In the Declaration, Dr. Davidson establishes the following:

1. Images of the claimed cell line are shown in **EXHIBIT C** of the Declaration. Specifically, **EXHIBIT C** sets forth two light microscopic images of cells from a transformed human adult cardiomyocyte cell line designated "AC16" (panel (a)) and a transformed human fetal cardiomyocyte cell line designated "RL14" (panel (b)). Both the AC16 and RL14 cell lines are immortalized human undifferentiated cardiomyocyte cell lines. The AC16 cells were generated by fusing post-mitotic primary non-immortalized human cardiomyocytes obtained from primary adult human ventricular tissue with ethidium bromide-treated, human SV-40-transformed mitochondrial DNA-free (rho zero) fibroblasts. The RL14 cells were generated by fusing post-mitotic primary non-immortalized human fetal cardiomyocytes with the same ethidium bromide-treated, human SV-40-transformed mitochondrial DNA-free (rho zero) fibroblasts used to generate the AC16 cells. The only difference between the AC16 and RL14 cell line production methods was the use of primary cardiomyocytes at developmentally different stages (i.e., adult or fetal). Adult stage primary cardiomyocytes were used to generate the AC16 cell line, and fetal stage primary cardiomyocytes were used to generate the RL14 cell line.

2. The claimed cell line, whether derived from adult or fetal primary cardiomyocytes, possesses certain morphological characteristics. As shown in **EXHIBIT C**, the AC16 and RL14 cell lines are characterized by homogeneous cells which (a) are evenly-shaped, (b)

have large central nuclei and (c) have a larger average ratio of nucleus volume to cytoplasm volume than do native primary human cardiomyocyte cells. Both AC16 cells and RL14 cells are also smaller in size relative to native primary human cardiomyocytes.

3. Figures 1 and 5 of Wang show the W1 cell line. In contrast to the claimed cell line, the W1 cell line shown in Figures 1 and 5 of Wang contains heterogeneous, refractile, spindle-shaped cells. The cells of the W1 cell line morphologically resemble native human primary cardiomyocytes. Wang states that the W1 cell line "has been shown to share morphologic and phenotypic characteristics with native human fetal cardiomyocytes," that W1 cells "look very similar" to native primary cardiomyocytes under light and electron microscopy, and that "by morphologic criteria these two types of cells [W1 cells and human fetal cardiac myocytes] are indistinguishable from one another." Wang, page 73, column 1, ¶1; page 66, column 1, 2nd full paragraph; and page 66, legend for Figure 1, respectively.

4. A comparison of morphologies of the claimed cell line (described in paragraphs 8 and 9) and the W1 cell line of Wang (described in paragraph 10 above) reveals that these two cell lines are morphologically different, and therefore, not the same.

5. The claimed cell line and the W1 cell line of Wang also have different growth characteristics. **EXHIBIT D** of the Declaration sets forth growth curve data obtained from an experiment using AC16 cells. In this experiment, 5 X $10^4$ cells of each of the three cell types (AC16, control fibroblasts and DWFb1$\rho^0$ (human SV-40 transformed mitochondrial DNA-free [rho zero] fibroblasts)) were seeded in 10 ml of growth medium in multiple 10 $mm^2$ dishes. For AC16 cells, DMEM/F12 supplemented with 12.5% FBS was used, and for control fibroblasts, MEM supplemented with 15% FBS was used. To support the growth of DWFb1$\rho^0$ cells, medium was used which consisted of the fibroblast medium and uridine at 50µg/ml. At 24-hour time intervals, cells from individual plates were trypsinized and counted. AC16 cells continued to divide until the $6^{th}$ day. Proliferation of AC16 cells slowed as the cells approached confluence, similar to the observed proliferation of control primary fibroblasts. The calculated doubling time was 24.49 hours for the AC16 cells, 23.91 hours for the control fibroblasts and 23.09 hours for the DWFb1$\rho^0$ cells.

6. Wang states on page 66, column 2, $1^{st}$ full paragraph, that the W1 cell line has a doubling time of 55.4 hours. This doubling time is more than twice as long as the 24.49 hour doubling time of the claimed cell line.

7. Based on the morphological and doubling time differences described above, the claimed cell line is not the same as the W1 cell line of Wang.

Given that the claimed cell line is not the same as the W1 cell line of Wang, as established by the annexed Declaration, Wang et al. fails to anticipate the cell line of claims 1 and 3-5. The Examiner has not established any teaching to the contrary.

In view of the above remarks, applicant maintains that claims 1 and 3-5 satisfy the requirements of 35 U.S.C. §102(b).

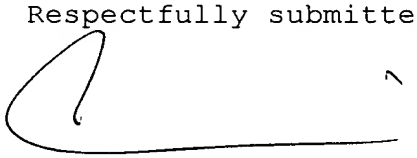
**Summary**

Applicant maintains that the claims pending are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $55.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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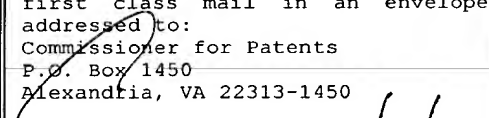

1/21/04
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